U.S. DEPARTMENT OF COMMERCE
National Technical Information Service

PB-252 746-T

THE MINERAL CONTENT OF THE ARTERIAL WALL OF INFANTS AND ITS RELATION TO ARTERIAL CALCINOSIS IN CHILDHOOD

Environmental Protection Agency

1973

141031

PB 252 746-T

TR 375-74

G. Brandt, K.B. Kortmann

THE MINERAL CONTENT OF THE ARTERIAL WALL OF INFANTS AND ITS RELATION TO ARTERIAL CALCINOSIS IN CHILDHOOD

[Der Mineralgehalt der kindlichen Arterienwand und seine Beziehung zur kindlichen Arterienkalzinose]

Beitr. Path., Vol. 150, 1973, pp. 274-286

Translated for the
ENVIRONMENTAL PROTECTION AGENCY
by
Translation Consultants, Ltd., Arlington, Virginia

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

BIBLIOGRAPHIC DATA SHEET	1. Report No. EPA TR 74-375	2.	3. Recipient's Accession No.
4. Title and Subtitle Mineral Content of the Arterial Wall of Infants and its Relation to Arterial Calcinosis in Childhood.			5. Report Date 1973 6.
7. Author(s) G. Brandt, K. B. Kortmann			8. Performing Organization Rept. No.
9. Performing Organization Name and Address Translated from the German by EPA			10. Project/Task/Work Unit No. 11. Contract/Grant No.
12. Sponsoring Organization Name and Address EPA ISD Translation Services Library RTP, NC 27711			13. Type of Report & Period Covered 14.

15. Supplementary Notes

Beitr. Path, 150:274-286 (1973)

16. Abstracts

17. Key Words and Document Analysis. 17a. Descriptors

Heart Disease
Calcium
Trace Elements

17b. Identifiers/Open-Ended Terms

Cardiography
Heart Diseases
Pediatrics
Trace Elements
Zinc
Calcium
Arterian Calinosis

17c. COSATI Field/Group 06-E

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages
Exclusive permission granted to NTIS for the storage and distribution of this material.	UNCLASSIFIED	18
	20. Security Class (This Page) UNCLASSIFIED	22. Price 3.50

G. Brandt, K.B. Kortmann

THE MINERAL CONTENT OF THE ARTERIAL WALL OF INFANTS AND ITS RELATION TO ARTERIAL CALCINOSIS IN CHILDHOOD

Calcifications of the inner elastic membrane are the earliest occurring changes in human arteries and detectable even in infancy (W.W. Meyer, 1968). The favorite places for these frequent calcium deposits are the distal aortas, the iliac arteries, and the internal carotid artery (Meyer and Lind, 1971). Whereas the inner elastic membrane shows strip-like calcifications in the aorta, they are arranged in arteries of the muscular extremities preponderantly around the so-called spindles and show pathogenetic relationships to the origin of Moenckeberg's media calcification (Meyer and Stelzig, 1967).

The pathogenesis of this early form of arterial calcinosis is not explained. It possibly is concerned with a phenomenon similar to calciphylaxis in which exogenous factors such as food and an increased loading with vitamin D sensitize the calcium metabolism for calcium deposits, and local increased mechanical loading of the wall provokes, as "challenger," the calcium deposits at specific places (Selye, 1962; W.W. Meyer, 1968).

Arterial calcifications produced experimentally using the model of calciphylaxis (Seifert and Dreesbach, 1966; Seifert and Dulawa, 1969) show morphological similarities with the early forms of human arterial calcinosis. In this experimental model, systematically applied manganese and zinc salts inhibit the formation of arterial calcinosis (Drescher, 1969). The development of experimental calcification of the cardiac apparatus can be inhibited by supplies of manganese and zinc (Riesner and

Seifert, 1972). In this case, it is uncertain whether the effect of inhibiting calcification represents a local reaction or a general metabolic effect. Selye (1962) sees a local inhibiting effect in the prevention of the calciphylactic reaction. Hilmers (1971) indicates the absence of calcium deposits when supplying manganese or zinc cells as a consequence of a general effect on the phosphate metabolism.

A local effectiveness of concentrations of these base elements in the arterial wall had to be shown in a reduced calcium content. Zinc and manganese must form reciprocal relationships with respect to calcium.

Quantitative mineral analyses of the juvenile arterial wall are not yet available as far as we know. For this reason, the calcium and trace element content of the juvenile arterial wall should be determined. Along these same lines, it should be tested to establish the local relationships between calcium content and trace element content.

Material and Methods

The investigations involved the arteries of 43 male and female deceased persons from the current autopsy group, ranging in age from 5 months to 20 years (Tables 1, 2). With all autopsies, a washing of the arteries with tap water was strictly avoided in order not to introduce error into the quantitative result.

With 12 cases, the abdominal aorta was processed histochemically with the iliac arteries (in five cases, additionally also with the internal carotid artery). The arteries were taken out and fixed in 80% alcohol, then bedded in paraffin and cut into sections. The histochemical demonstration of calcification took place according to Voigt (1957).

The following arterial sections were investigated in 31 cases (for technical reasons, only one localization with three cases and two localizations with six cases, total 2): abdominal aorta, right and left iliac artery, right and left internal carotid artery. After a brief fixation in 80% alcohol, marginal sections were taken from each sample and imbedded in paraffin. The histochemical proof of calcification was carried out according to Voigt (1957) on five nm thick sections. The adventitia of the arterial segments was removed with a pair of tweezers. Fat was removed from the samples in acetone. They were then dried to constant weight at a temperature of 90°C, wet ashed and dissolved in a 5% lanthanum chloride solution. The elements calcium, magnesium, copper, manganese, zinc and cobalt were measured using the Beckman 495 atomic absorption spectrometer against aqueous standard solutions and calculated as mg element per gram fat-free dry tissue. The statistical computation was carried out by means of regression-correlation analysis.[1]

Edge pieces were taken from five internal carotid arteries and ground up and 6 mg of the resulting dusty material was then processed with 800 mg potassium bromide to a compact. This was investigated for crystal precipitations using the Beckman IR10 infrared spectrometer.

The autopsy of the 31 analytically investigated cases was carried out 12-28 hours after death. The bodies were kept under refrigeration. Cases with hemolysis (bloody diffusion of the intima) which had been recognized from clinical symptoms or from the clear hemolysis during section were not

---

1. We express our appreciation to Professor Dr. Horbach and Mr. Prestele (Institute for Medical Statistics and Documentation of the University Erlangen-Nuremburg) for their advice and assistance.

taken up by the study group.

An essential autolysis of the components of the vessel walls is not to be expected in this period after section. The measured trace elements appearing in the tissue not as free metals but as metal-organic compounds will accordingly not modify their concentration post-mortally by diffusion or other physical-chemical processes. A false positive modification of concentration by diffusion by the surrounding area in the arterial wall is not to be expected with the selected localization without the association of parenchymatous organs with high trace concentrations. The autopsies made shortly after death in the described preparation technique guarantee a sharply localized histochemical picture of calcium salt precipitates.

The investigations allow conclusions to be made as to the concentrations of elements in the living child, of course with the proviso that the basic illnesses leading to death could pathologically affect the calcium and trace element metabolism in varying degrees. Our study group is too small to make a statement as to such etiological factors.

Findings

1. Histochemical Investigations

The histochemical proof of calcium according to Voigt (1957) in the case of 12 extracted aortal and iliac arteries revealed in five cases granular to strip-like precipitations of calcium along the internal elastic membrane of the iliac arteries (Figure 1). The calcium depositions were found only on short stretches to the membrane and were freq uently localized on the edge of membrane fissures. It was possible to show in seven cases by histochemical methods that there was no precipitation of calcium salts.

In two cases (36 and 41, Table 1) finely divided, dust-like reaction products were accumulated in the media without any localized calcium depositions. These reaction products were also to be found in the general area of calcium precipitations along the internal elastic membrane. We evaluated these pulverulent positive reactions with the greatest of care since the finding of the calcium proof is a decided function of the type and duration of fixation (Voigt, 1967; Brandt, 1971). In the case of a uniform loading of the tissue with pulverulent reacting products, there frequently occurs a "false positive" reaction (Brandt, 1971). The histochemical investigation of the relatively small edge sections of the 31 cases which were processed on a chemical-analytical basis resulted in only a minimum picture of calcium salt precipitations. Out of 28 aortas investigated, we found only one case (18, Table 2) in which the innermost elastic membrane was diffused with calcium salts for a short section. In 58 sections of iliac arteries which were investigated histologically, we find the proof of calcium positive in 14 cases whereas, in 48 sections of the internal carotid artery, we found the calcium detection 23 times positive. By positive is meant here, the extremely fine particle depositions which are strictly limited on a local basis to the internal elastic membrane (Figure 2) and which could be significantly delimited by an unspecific reaction. Coarse calcium precipitates and negative calcium detection occurred at all levels.

Figure 1. Calcium deposition in the internal elastic membrane of the internal carotid artery (alcohol-fixation; Voigt-reaction. X 440).

Table 1. Survey of 12 histochemically investigated cases (case number - age - sex + = positive reaction).

case	age	sex	basic ailment	histological calcification	
32	1 y	♀	Akute Leukose	1	–
33	1,3 y	♀	Vorhofseptumdefekt	2	+
34	12 y	♂	Sepsis	3	–
35	8 y	♀	Leukose	4	–
36	10 y	♂	Fallot IV	5	+
37	6 Mo.	♂	Fallot IV	6	–
38	6 y	♂	Hyperpyrexie	7	–
39	4 y	♀	Fallot III	8	+
40	14 y	♀	M. Werlhoff	9	+
41	20 y	♀	Bronchopneumonie	10	–
42	8 y	♀	Leukämie	11	+
43	1 y	♂	Herzmißbildung	12	–

Key to column 4.

1 - acute leucosis; 2 - defect of auricular septum; 3 - sepsis; 4 - lucosis; 5 - Fallot IV; 6 - Fallot IV; 7 - hyperpyrexia; 8 - Fallot III; 9 - Werlhoff's desease; 10 - bronchial pneumonia; 11 - leukemia; 12 - cardiac malformation;

Table 2. Survey of 31 analytically investigated cases (calcium content in mg calcium/g fat-free dry weight).

case	age		basic ailment 3	Aorta 1	Kalziumgehalt in Beckenarterien 1	Karotissiphon 2
1	10 Mo.	♂	Herzmißbildung	0,40	0,72/0,73	2,1 /2,5
2	5 J	♂	VSD	0,41	0,67/1,52	Ø
3	5 J	♂	Wilmstumor	0,41	0,6 /0,7	Ø
4	2 J	♂	Hirntumor	0,48	0,65/0,67	1,64/1,67
5	5 Mo.	♀	Plexuspapillom	0,51	0,8 /1,0	Ø
6	1 J	♂	Salmonellose	0,52	0,6 /0,7	0,9 /1,99
7	4 J	♂	Sepsis	0,53	0,53/0,59	24,0/32,0
8	3,5 J	♀	Akute Leukose	0,53	0,69/0,96	2,93/6,5
9	10,5 J	♂	Enzephalitis	0,54	0,57/0,75	1,84/2,35
10	3 J	♂	Hirnabszeß	0,57	0,82/1,32	2,04/2,31
11	5 Mo.	♂	Hydrozephalus	0,64	0,6 /0,6	1,7 /8,5
12	9 J	♀	Enteritis	0,65	0,93/1,0	5,27/7,28
13	7 J	♀	M. Roger	0,67	0,69/1,06	2,08/3,75
14	6 J	♀	Herzmißbildung	0,71	0,70/0,75	0,95/1,05
15	9 Mo.	♀	M. Fallot	0,82	1,18/1,34	5,77/8,33
16	19 J	♂	Akute Leukose	0,84	0,98/1,08	1,24/9,96
17	1,5 J	♂	Hydrozephalus	0,89	0,75/0,82	2,72/19,12
18	9 Mo.	♀	Hirnschaden	0,89	0,90/1,07	Ø
19	5 J	♀	Hirntumor	0,98	0,74/0,83	1,04/1,18
20	6 Mo.	♂	Schädelmißbildung	1,01	1,2 /1,5	2,0 /2,4
21	13 J	♀	Lymphosarkom	1,01	0,77/0,99	1,5 /14,15
22	7,2 J	♂	Mukoviszidose	1,04	0,96/0,96	12,8/18,4
23	7 Mo.	♂	Mukoviszidose	1,16	1,19/1,72	34,0/97,2
24	9 Mo.	♀	Glykogenspeicher-krankheit	1,17	1,27/1,51	6,09/8,9
25	17 J	♂	Sepsis	1,47	1,05/1,21	Ø
26	6 Mo.	♂	Mißbildungen	1,48	1,88/1,97	5,08/5,49
27	20 J	♂	Sepsis	3,67	0,77/1,20	Ø
28	10 J	♀	Fallot V	6,81	1,02/1,03	3,49/52,5
29	4 Mo.	♂	Mesenchymom	Ø	Ø	3,9 /31,3
30	12 J	♂	Leukämie	Ø	Ø	2,0 /3,56
31	7 J	♂	Lymphosarkom	Ø	4,33/4,7	Ø
no. of investigated test samples.				n = 28	n = 58	n = 48

Key: 3 - column 3; top to bottom.

1 - calcium content in iliac arteries; 2 - internal carotid artery; 3 - cardiac malformation; VSD; Wilm's tumor; brain tumor; plexal papilloma; salmonellosis; sepsis; acute leukosis; encephalitis; brain abscess; hydrocephalus; enteritis; Roger's defect; cardiac malformation; Fallot's defect; acute leukosis; hydrocephalus; brain damage; brain tumor; cranial malformation; lymphosarcoma; mucoviscidosis; mucoviscidosis; glycogen storage disease; sepsis; malformations; sepsis; Fallot V; mesenchymoma; leukemia; lymphosarcoma.

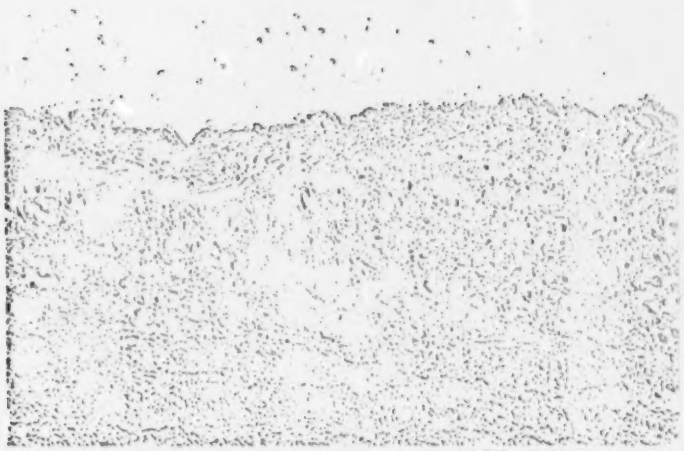

Figure 2. Mineralization and beginning calcification of the internal elastic membrane of an iliac artery (alcohol fixation, Voigt-reaction; X_{330}).

2. Results of chemical-analytical investigations

The mean values of the mineral contents obtained by analytical methods are listed in Table 3 according to the locations aorta, iliac and internal carotid artery. The internal carotid artery has on the average the highest of mineral contents out of all the elements investigated. All elements investigated revealed, according to the Friedman test, significant differences in the three vessel areas and the error probability amounted to 0.1% at any given time. The test method of Wilcox and Wilcoxon was included in this total test in order to evaluate the mutual differences of element concentrations in the three vessel areas investigated. These mutual comparisons revealed, in the case of calcium, magnesium, copper, cobalt and manganese similar results and, in actual fact, significant differences between the internal carotid artery on one hand, and the aorta and iliac on the other hand. The content of these elements in the aorta and iliac revealed no certain differences. In the case of zinc however, the result

was otherwise. In this case, a difference was found between the aorta and iliac as well as between the aorta and the carotid artery with, again, no difference between iliac and internal carotid artery.

Out of the 28 aortal test samples analyzed, 26 contained between 0.4 and 1.5 mg calcium per g dry tissue. In the case of one 20-year-old man, with a sepsis, increased values of 3.5 mg[1] per g were measured. There was also the case of a 10-year-old girl with a Fallot's tetralogy where increased values of 6.5 mg[1] per g were measured. No depencency of age and calcium content of the juvenile wall was found. The magnesium as well as the zinc contents are high (0.25-0.77 and 0.778-0.36 mg per g respectively). Both show, as does manganese, a positive correlation to the calcium content (Table 3a, Figure 3). Cobalt shows no statistically assured increase with rising calcium content.

Table 3a. Mineral content (x = mean value, s = standard deviation) of juvenile aortae, iliac and carotid arteries).

localization	Aorta		iliac		internal carotid artery	
	x	s	x	s	x	s
calcium	0,79	0,31	0,97	0,31	9,01	13,91
magnesium	0,28	0,09	0,30	0,13	0,53	0,30
zinc	0,15	0,07	0,10	0,09	0,27	0,14
copper	0,11	0,27	0,15	0,35	0,16	0,19
cobalt	0,0028	0,0022	0,0050	0,0043	0,0093	0,0073
manganese	0,0030	0,0013	0,0026	0,0019	0,0057	0,0061

1. According to the criteria for runaway values of Pearson and Stephens, these values were omitted in the statistical computation.

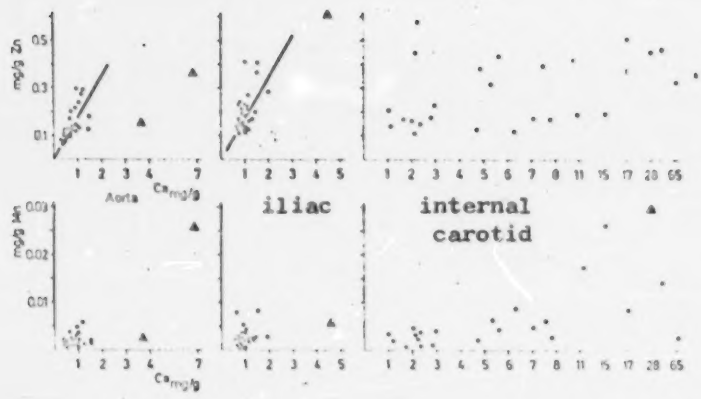

Figure 3. Scattergram of calcium content and zinc/manganese content of juvenile aorta, iliac and internal carotid artery (n = 28).

The calcium content of 58 iliac arteries analyzed ranges between 0.53 and 1.97 mg calcium per g dry tissue. The iliac arteries of a 7-year-old boy with a lymphosarcoma treated intensively by radiation therapeutic and cytostatic methods (case 31, Table 2) have a calcium content of 4.33 or 4.7 (1) mg calcium respectively per g. Zinc and magnesium likewise provide, as do manganese and cobalt, a positive correlation (Table 3b, Figure 3). The copper content shows large differences as in the case of the aortas. A dependency of calcium content and age could not be detected in the period investigated.

The calcium content of the internal carotid artery fluctuates considerably from case to case. The differences with the remaining locations are great. The differences between the right and left internal carotid artery are usually in a comparable relationship (Table 2). The contents of magnesium, zinc, manganese, and cobalt and the carotid wall also actually reveal a positive correlation to the calcium content. Indeed, it was found possible

to establish a linear dependency for magnesium, a 1% probability over all.

Table 3b. Correlation of calcium and the indicated elements in juvenile aortae, iliac and internal carotid arteries (** linear correlation on 1% level, * linear corellation on 5% level, - no linear correlation).

	Aorta	iliac	cartorid artery
magnesium	0,69 **	0,40 *	0,73 **
zinc	0,37 **	0,49 *	0,24 —
copper	0,16 —	0,22 —	0,18 —
cobalt	0,25 —	0,65 **	0,11 —
manganese	0,18 —	0,17 —	0,19 —

The occasionally considerable degree of depositions of calcium salts in the carotid artery wall reveals that the trace elements investigated take part in the mineralization and no reciprocal relationships in mineral contents could be uncovered. It was also not possible to determine in this localization any tendency of calcium salts and age.

The copper content of the arterial wall shows striking individual differences. With 6 cases (7, 16, 18, 20, 28, 29, Table 2) the copper content ranged between 0.6 and 1.6 mg per g whereas it otherwise only ranged between 0.0045 and 0.05 mg per g of dry weight. With 5 cases, all investigated arteries had this high copper content. In the case of a 4-year-old youth (case 7, Table 2) with a sepsis following appendicitis, only the carotid artery heavily incrusted with calcium showed an increased copper content whereas the aorta and iliac arteries revealed no copper concentration. Age, sex, and basic illness gave no clue to the etiology of the high copper content. It was possible to establish connections to copper storage disease by the comparison with an analytically assured Wilson's disease of a 17-year-old girl (autopsy No. 288/72) with an arterial copper ranging between 0.16 and 0.22 mg per g.

3. Results of Infrared Spectroanalytic Investigations

The infrared spectra of pulverulent material from ground-up carotid sinus tissue show clear resorption strips and their impression just as obtained in the investigation of dried and fat-extracted bone meal. At the same time, the typical pattern of apatite is superimposed through absorptions of the remaining organic components. From this finding, it may be concluded that coarser calcium depositions in the juvenile arterial wall are present in the form of apetite.

Discussion

Calcifications in the elastic membrane of juvenile arteries as described by Meyer and Stelzig (1967), were demonstrated by the histochemical investigation of 12 arterial preparations using an appropriate fixation technique. The relatively slight percentage of observed calcifications is considered a consequence of the selected investigative technique. Using the modified microscopic Kossa reaction (Meyer and Stelzig, 1969), it was possible to microscopically view the entire arterial tube. There were also smaller carbonite and phosphate precipitates detected when giving a sufficiently long exposure in silver nitrate solution. Nevertheless, since according to investigations with the microprobe (Herbst, et al., 1971), the calcium depositions and silver salt precipitates in the Kossa reaction are not identical, we only carried out the histotopochemical calcium proof according to Voigt (1957) following sufficient alcohol fixation and avoiding the contamination of the tissue with tap water. This was done in order to avoid false "positive" reactions (Brandt, 1971). At the same time, we only observed in two cases a dusty tinting of the media after a somewhat

longer lasting alcohol fixation. This diffuse dusty positive reaction often occurs after an insufficient fixation and is to be judged quite carefully.

A topographical distribution pattern of the elastic calcifications can naturally not be revealed by the processing of material preparations in steps.

The quantitative analysis of material walls with the result of significant differences between iliac arteries and aortas on one hand, and internal carotid artery on the other hand, indicates that the physiological construction of the wall conditions a differing mineral content. A differing content can be found in the smooth muscle system and in elastic fibers. Corresponding to the high calcium content, histochemically detectable calcium depositions are more frequently found in the internal carotid artery than in the iliac arteries and in the aorta. The finding of the thoroughly positive correlation between calcium and trace elements signifies a common participation of all elements investigated in the mineralization of the arterial wall. The calcification inhibiting effect of manganese and zinc irons on arterial calcinosis in the calciphylactic experiment is explained according to the calcification theory of Urist, et al. (1946) as a competitive inhibition of the initial calcium deposition in the elastin transferrent into elastoid. Accordingly, a reciprocal behavior of these elements and the calcium content must be expected. The positive correlation (Figure 3) of the manganese and zinc content to the calcium content found in all three locations in the arteries investigated by us suggests, nevertheless, against this hypothetical significance of the effect of a systemic zinc or manganese salt supply over a local competitive inhibition. Quantitative determinations

are not as yet available to support this hypothesis.

The opinion of other authors is that phosphate metabolism has a decisive influence on the initial stage of calcification. Accordingly, the calcium deposition is not the primary stage but phosphorylation probably precedes calcification (Eger, 1963; Krane and Glimcher, 1965; Seifert, 1968). Hilmers (1971) was able to prove that with calciphylactic arterial calcinosis the hyperphosphatemia appearing normally with dikydrotachysterin does not occur with systemic application of zinc and manganese salts. Calcium depositions in the arterial wall are thereby considerably prevented in spite of a rise in blood calcium.

Insofar as the pathogenesis of the calcinosis of the juvenile arterial wall is concerned, the trace elements accordingly have meaning only insofar as they participate in the mineralization of the arterial wall. This finding of the general mineralization with the process of calcium deposition appears to correspond to a general principle; i.e., Reif and Lange (1972) were able to demonstrate the participation of trace elements with the mineralization and calcification of necrobiotic kidney epithelia during experiments with animals. According to infrared spectroanalytic investigations, calcium depositions and juvenile arteries are concerned with apatite. Apatite had already been found as a mineralization product in human aortas by Yu and Blumental (1963).

The determinations of the trace elements provide no explanation for the etiology of the calcinosis of the arterial wall. A prerequisite for the precipitation of salts is an exceeding of the solubility product which is not achieved for calcium phosphate with physiological serum concentrations, and is quite to the contrary, heavily reduced by the presence of "nucleic-

involved collagens" (Fleisch, 1961). Since children have, in contrast to adults, a hyperphosphatemia in a physiological sense with normal serum calcium values (Documenta Geigy, 1969; Keller-Wiskott, 1966), it is possible that the high level of serum phosphate prepares the way for juvenile arterial calcinosis. Vessel areas with special mechanical alteration, as for example the internal carotid artery, then form the initial location of the calcium precipitates through a slight modification of the structure of the elastic membranes together with formation of crystallization nuclei. This then takes place as a kind of chain reaction (Seifert, 1965, 1968).

The significance of juvenile arterial calcinosis as a function of an individually differing pronounced hyperphosphatemia makes understandable the situation whereby there results no dependency of calcium content of the arterial wall and age of the person concerned in the period investigated and that cases of pronounced arterial calcinosis are already found in infancy. The significance indicates that the degree of calcinosis can be dependent on exogenous nutritional factors, for example, the composition of the milk food (Oppe, et al., 1968). Support for this position is also found in that cases of pronounced arterial calcinosis have been observed with juvenile otherwise healthy accident deaths (W.W. Meyer, 1968). Calcium depositions in considerable amounts in the internal carotid artery in the case of inherent metabolic defects indicate a participation if endogenous metabolic disturbances (glycogen storage disease, case 24; mucoviscosis, cases 21 and 22, Table 2).

BIBLIOGRAPHY

Brandt, G., Report XV, Symposium der Ges. für Histochemic, Düsseldorf, 1971, Acta Histochem. Suppl.,(in press)

Drescher, S., Beitr. Path. Anat., Vol. 139, 1969, p. 74.

Documenta Geigy: Scientific Tables (Wissenschaftliche Tabellen) Basel, 1969.

Eger, W., Verh. Dtsch. Ges. Inn. Med., Vol. 71, 1965, p. 533.

Fleisch, H., Schweiz. Med. Wschr., Vol. 29, 1961, p. 858.

Herbst, R., Multier, A.M., Krönicher, W., Zbl. Allg. Path., Vol. 114, 1971, p. 589.

Hilmers, G., Dissertation, Hamburg, 1971.

Glimcher, M.J., Krane, S.M., Radioisotopes and Bone, McLean, R., Budy, A.M., Oxford (1962).

Keller, W., Wiskott, A., Lehrbuch der Kinderheilkunde, [Textbook of Pediatrics], Thieme, Stuttgart, 1966.

Meyer, W.W., Stelzig, H.H., Virchows Arch. Path. Anat., Vol 342, 1967, p. 361.

Meyer, W.W., Beitr. Path. Anat., Vol. 138, 1968, p. 149.

Meyer, W.W., Lind, J., Kinderheilk, Vol. 23, 1971, p. 238.

Oppe, T.E., Lancet I, 1968, p. 1045.

Reif, W., Lange, H.P., Beitr. Path., Vol. 145, 1972, p. 221.

Riesner, K., Seifert, G., Virch. Arch. Abt. A Path. Anat., Vol. 355, 1972, p. 118.

Seifert, G., Dtsch. Med. Wschr., Vol. 90, 1965, p. 2334.

Seifert, G., Arztl. Praxis, Vol. 20, 1969, p. 1.

Seifert, G., Dreesbach, H.A., Frankf. Z. Path., Vol. 75, 1966, p. 342.

Seifert, G., Dulawa, A.G., Beitr. Path. Anat., Vol. 139, 1969, p. 59.

Selye, G., Calciphylaxis, The University of Chicago Press, Chicago (1962).

Urist, M.R., Moos, M.J., Adams, J.M., Arch. Path, Vol. 77, 1964, p. 594.

Voigt, G.E., Acta Histochem., Vol. 4, 1957, p. 122.

Yu, S.Y., Blumenthal, T., Lab. Invest., Vol. 12, 1963, p. 1154.